Clinical

Laboratory

Improvement

Advisory

Committee

Subcommittee Meeting on Proficiency Testing,
Quality Assurance and Quality Control

August 30, 1995

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

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Quality Assurance and Quality Control

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Summary

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Record of Attendance

The Clinical Laboratory Improvement Advisory Committee (CLIAC) Subcommittee on Proficiency Testing, Quality Assurance and Quality Control met at the Swissôtel, 3391 Peachtree Street, in Atlanta, Georgia, on August 30, 1995. Those in attendance are listed below:

Committee Members
Dr. Wendell O'Neal
Dr. Paul Bachner
Dr. Susanne Gollin
Dr. Verlin Janzen
Dr. Bereneice Madison
Dr. Morton Schwartz

Ex Officio Members
Dr. Carlyn Collins, CDC
Dr. Steve Gutman, FDA
Ms. Judith Yost, HCFA

Executive Secretary
Dr. Edward Baker

Non-voting Liaison Representative
Dr. Fred Lasky (HIMA)

Centers for Disease Control and Prevention

Ms. Nancy Anderson
Dr. John Astles
Ms. Rosemary Bakes-Martin
Ms. Louise Barden
Ms. Carol Bigelow
Dr. Joe Boone
Ms. Sheila Boring
Ms. Gail Bosley
Ms. Diane Bosse
Ms. Genoria Bridgeman
Ms. Cheryl Coble
Ms. Debbie Coker
Ms. Crystal Frazier
Ms. MariBeth Gagnon
Ms. Sharon Granade
Mr. Tom Hearn
Mr. Edwin Holmes
Dr. Adam Manasterski
Dr. John C. Ridderhof
Ms. Eunice Rosner
Mr. Darshan Singh
Ms. Elva Smith
Mr. Gregory Smothers
Dr. Tina Stull
Ms. Julie Wasil
Ms. Glennis Westbrook
Ms. Rhonda Whalen

Welcome and Announcements

Dr. Wendell O'Neal, Chairman of the Subcommittee on Proficiency Testing (PT), Quality Assurance (QA) and Quality Control (QC), called the meeting to order. The subcommittee members were welcomed by Dr. Edward Baker, Director of the Public Health Practice Program Office, CDC, and Executive Secretary of CLIAC. Announcements and charge to the Committee were made by Dr. Morton Schwartz, Chairman of CLIAC, who participated in the subcommittee meeting in the absence of Dr. Glenda Price. Dr. Schwartz reminded the members that the Subcommittee is advisory to CLIAC, which is advisory to the Department of Health and Human Services (DHHS).

The following topics were scheduled for subcommittee discussion: (1) requirements for test method verification and (2) appropriate materials for QC testing. Prior to the meeting, copies of overheads of the presentations and the CLIA QC regulations were provided to the CLIAC members.

Requirements for Test Method Verification — Addendum A

Ms. Rosemary Bakes-Martin, of the CDC, provided background information on the current requirements for test method verification and described the CDC proposed requirements for verifying test system performance. During the current phase-in of the QC requirements, laboratories performing unmodified, moderate complexity tests cleared by the FDA through the 510K/PMA process are not required to perform test method verification. Laboratories performing high complexity tests, moderate complexity tests modified by the laboratory, or moderate complexity tests using test systems not cleared by the FDA are required to verify or, as appropriate, establish test system performance prior to use. When the phase-in expires on September 1, 1996, all laboratories would be required to meet the same set of QC standards.

During the QC phase-in, the FDA was to establish a process to review manufacturer's QC instructions for CLIA compliance. The intent of this provision in the regulations was to allow laboratories, using test systems cleared by the FDA (as meeting the CLIA QC requirements), to meet the CLIA requirements by following the manufacturer's instructions, including test method verification protocols. However, the FDA was not able to implement the QC clearance process. Therefore, under the current regulations, when the phase-in expires, all laboratories would need to verify test method performance prior to reporting patient test values.

In response to numerous comments which indicated that laboratories are unclear about what is required to verify a test system prior to use, and comments that the

current requirements appear excessive and unreasonable for moderate complexity tests, Rosemary Bakes-Martin described a CDC proposal to establish separate, explicit requirements for moderate and high complexity testing. Under the proposal, all laboratories would be required, at minimum, to verify the accuracy, precision and reportable range of the test method; additional requirements would be specified for high complexity procedures and laboratory-modified or laboratory-developed test methods. By identifying the minimum requirements for test method verification, the requirements would be less subjective, and laboratories would still be able to design their own protocols, thus allowing flexibility and accommodation for new technologies. The general verification requirements for moderate and high complexity testing would need to be supplemented by specifying the alternatives and/or exceptions applicable to certain tests, such as microbiology procedures and qualitative tests.

Subcommittee Discussion

The Committee expressed confusion concerning the requirement to **verify** test method performance and the requirement to **establish** method performance specifications (**validation**), and requested definitions of these terms. To clarify the differences between "verification" and "validation," Ms. Bakes-Martin explained that validation is a more extensive process that would apply to laboratory-developed or "in-house" test procedures or commercial products modified by the laboratory.

There was a lengthy discussion about using a "1-box" vs. "2-box" model for QC requirements. One committee member felt that basing QC requirements on test complexity, i.e. a "2-box model," resulted in an artificial dichotomy which is inappropriate for the current or future spectrum of testing devices. Several subcommittee members agreed with a "1-box model," that would include establishing core requirements for verification of quantitative test methods. However, there was agreement that a mechanism should be established to deal with exceptions/alternatives for some tests, such as qualitative procedures and microbiology tests. In general, the subcommittee members agreed with a "1-box model" for QC requirements but felt that a "2-box" model, based on test complexity, is still appropriate for personnel requirements.

The subcommittee members agreed that laboratories should verify the manufacturer's claims for test performance before patient results are reported, but opinions differed as to how this should be accomplished. The Health Industry Manufacturers Association (HIMA) liaison agreed that laboratories should, in some way, verify that test systems perform acceptably in their laboratory environment. He noted that manufacturers currently provide information on test system performance and reportable range to the FDA to receive clearance for their

products. In addition, he indicated that the designer of the test system (manufacturer) has the best insight about how to verify the test system performance, and stated that the manufacturer should specify these procedures in the test system instructions. Some members felt that laboratories should follow the manufacturer's instructions for test method verification, while others were against total reliance on the manufacturer's instructions. These members felt that the regulations should identify the performance specifications to be verified by laboratories, but should allow laboratories flexibility in determining the verification protocols and should not inhibit the development of new technologies.

One committee member pointed out that the CLIA requirements apply to the laboratory, not to the manufacturer. Although he agreed that laboratories should verify test system performance, he was concerned that the current regulations do not provide adequate relief for large numbers of physicians' office laboratories that perform moderate complexity testing. He felt that at the end of the QC phase-in, laboratories using unmodified, moderate complexity, commercial test systems, would be required to verify accuracy, precision, sensitivity, specificity and the reportable range, which, in his opinion, would be too burdensome and costly.

Ms. Bakes-Martin reminded the Committee that in the proposal presented to the Committee, for unmodified, moderate complexity, commercial test systems, the laboratory would be required to verify only the manufacturer's performance claims concerning accuracy, precision and reportable range. In CDC's view, clarifying the verification requirements would provide regulatory relief to a large number of laboratories. Ms. Bakes-Martin reiterated that laboratories should verify that a test method performs acceptably and provides quality testing results **prior to reporting patient results**.

Additional discussion focused on the identification of the core requirements for test system verification. Opinions varied about the extent and methods to be used to verify the reportable range and whether sensitivity and specificity should be considered core requirements. One member recommended that laboratories verify accuracy, as defined by the manufacturer, and linearity throughout the reportable range. Some members expressed concern about the definition of "accuracy" and questioned whether the intent of the regulations was to verify accuracy or comparability. One member wanted to delete "accuracy" from the proposed core requirements. Ms. Bakes-Martin stated that definitions could be included in the regulations and presented the following CDC definitions of accuracy, precision and reportable range:

- **Accuracy**--the ability to obtain the expected result. This could be either defined by the manufacturer or the laboratory.

- **Precision**--the ability to repeat the expected result without significant day-to-day variation, i.e. repeatability.

- **Reportable range**--the range of values within which the accuracy of expected results can be assured.

Dr. Collins stated that the current regulations provide flexibility for test method verification, but many laboratorians want more specific guidance on how to verify test system performance. The committee members agreed that, whenever possible, verification methods should be simple and that some guidance should be provided. Members suggested providing guidance through various mechanisms. One member suggested that specific protocols could be provided as guidelines in the Health Care Financing Administration's State Operations Manual or could be developed and distributed by professional organizations or manufacturers, while another member was concerned that recommendations provided in guidelines may become mandatory requirements. A member commented that one laboratory accreditation organization has a set of general standards which apply to all laboratories and has developed checklists for determining compliance with accreditation requirements. The checklists are very procedure-oriented. The member noted that checklist items directed toward specific test methods, in effect, suggest protocols that would be viewed as requirements for compliance. The Subcommittee closed the discussion by making the following recommendations to the full CLIAC:

Recommendations

- The regulations should be descriptive, but not proscriptive i.e., requirements should be included, but not protocols for meeting the requirements.

- Prior to reporting results on patient specimens, laboratories should, at minimum, verify the accuracy, reproducibility and reportable range of the test method.

Appropriate Materials for QC Testing **Addendum B**

Dr. Tom Hearn of the CDC reviewed the current requirements for testing QC samples. He presented arguments for and against (1) changing the required minimum number of QC samples in an analytical run, from two to some other number, and (2) requiring that QC samples contain specific analyte concentration levels. He described the CDC proposal, to maintain the current requirement to test two QC samples of different levels, rather than specify concentration, per analytical run. Finally, he stated that the challenge for the laboratory is to ensure quality testing results in a cost effective manner, taking into consideration changes in technology.

Subcommittee Discussion

One committee member observed that the CDC proposal focuses on the testing "run" and on the conventional use of liquid samples. He thought that the requirement for testing two QC samples is appropriate, but that the samples should be at the upper and lower decision points, and that one sample would not be adequate. The committee member noted that the proposal does not address alternative QC approaches and indicated that it may be premature to establish alternative QC mechanisms.

The HIMA liaison disagreed stating that technologies are already in use that employ alternative QC procedures, and he provided the following information. Some manufacturers of the new technologies have data to support testing only one control per day. In addition, some test systems have internal, automatic sample controls, that check up to 80% of the testing process and exceed the CLIA requirement for testing QC each 24 hours. He noted that procedures could be established to monitor the remaining 20% of the testing process, which would be less burdensome. Also, some qualitative tests, developed since CLIA implementation, include controls with each patient test, which check up to 80% of the testing process, but do not check the extraction phase. He suggested that, since reagents have become more stable, using a control to check the extraction process with each new shipment or batch of reagents should be adequate. In addition, he indicated that there are problems with the regulatory definition of "run."

In response, one member recommended that the phrase "not longer than 24 hours" used in defining "run," be removed from the regulations and that laboratories perform QC testing in accordance with the frequency recommended by the manufacturer. Several members suggested that the definition of "run" and the frequency of testing controls should be topics for discussion at a future subcommittee meeting.

In discussing the number of QC samples, the Subcommittee rejected the option of requiring three controls as a minimum and agreed that running no controls would be inappropriate. One member felt strongly that the minimum number of QC samples should be one, while other members thought that running one or two controls could be appropriate depending on the technology of the test system. One member recommended maintaining the current requirement at two controls per analytical run, but stated that the concentration levels should be at the upper and lower medical decision points (or at different levels for analytes which have only one medical decision point). Some members doubted that manufacturers would be able to supply QC specimens at medical decision points for all tests. At the conclusion of the discussion, the Subcommittee made the following recommendations to the full CLIAC concerning QC samples:

Subcommittee recommendations

- Maintain the current requirement that two controls be tested per run.

- The regulations should not specify analyte levels in QC samples.

Public Comments

1. See Addendum C for statement given by Mr. Bill Moffitt, President of I-STAT Corporation.

2. Dr. Kevin D. Fallon, Director of Scientific Affairs, Instrumentation Laboratory, and Chairman of the NCCLS Subcommittee on Practical Blood Gas QC, said that QC has not been defined. He noted that the purpose of QC is to establish a statistical probability that the patient results are correct. He noted that QC of single test unit devices is different than QC of traditional test systems. With single use devices, in which each cartridge has an integral control, you make a reasonable assumption that the cartridge will give the correct answer. However, QC of an instrument has limitations. If the only thing wrong with the instrument is the part that determines whether the instrument is operating correctly, it will not be possible to establish a statistical probability that the instrument is working. His view is that QC performed by an instrument is not QC. The concept of QC must be broadened and QC programs must be designed to determine a statistical probability that a particular patient result is correct.

I certify that this summary report of the August 30, 1995, meeting of the CLIAC Subcommittee on Proficiency Testing, Quality Assurance and Quality Control is an accurate and correct representation of the meeting.

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Wendell R. O'Neal, Ph.D.
Chairman